## REMARKS

Prior to entry of this Amendment, Claims 1-29 were pending and under consideration. With this Amendment, Claims 5, 6, 9 and 27 have been canceled, without prejudice against their reintroduction into this or one or more timely-filed related applications, and Claims 1-4, 8-11, 14, 18-20, 22-24 and 29 have been amended. Thus, after entry of this Amendment, Claims 1-4, 7-8, 10-26 and 28-29 are pending and under consideration.

### The Amendments of the Specification

The specification has been amended to include two sheets of drawings including Figures 3, 4 and 6 (EXHIBIT A). As noted by the Patent Office, the instant application, which is a continuation of application Serial No. 09/373,347 (the "'347 application") was filed with four sheets of informal drawings, as evidenced by the attached copy of the postcard as stamped by the Patent Office (EXHIBIT B). Accordingly, Figures 3, 4 and 6 do not present new matter. It is also noted that the Figures 3, 4 and 6 are identical to Figures 3, 4 and 6 of the parent '347 application.

### The Amendments of the Claims

Claims 5, 6, 9 and 27 have been cancelled.

Claim 1 has been amended to refer to a "polypeptide" instead of "an amino acid" in the preamble. Support for the use of the term "polypeptide" is found in original Claim 1.

Claims 2, 4 and 8 have been amended to include the phrase "or said first library of altered target nucleic acids" in order to clarify the nucleic acids being contacted. Support for this amendment is found at page 26, lines 22-31 and on page 29, lines 1-14.

Claims 1, 2, 3 and 4 have been amended to include the phrase "whereby said first predetermined sequence undergoes domain specific gene evolution," which relates back to the phrase "gene evolution" in the preamble. In addition, Claim 3 has been amended to clarify that the recombination intermediate is contacted with a single strand-specific nuclease to form a nicked target nucleic acid. Support for this amendment is found throughout the specification as originally filed and specifically at, for example, page 30, lines 18-30.

For consistency with the other claims, Claim 8 has been amended to delete the expression "adding to" in favor of "contacting."

Claim 10 has been amended to delete the phrase "said library of altered target nucleic acids" in favor of "the resultant product" in order to more clearly identify the nature of the nucleic acid that is being introduced into cells.

Claim 11 has been amended to clarify the nature of the library that is being expressed and now refers to a "cellular" library. Support is found at page 6, lines 8-11.

Claims 14 and 23 have been amended to correct obvious errors in antecedent basis. Claim 23 has additionally been amended to correct a spelling error in the word "complementarity." Support for this amendment is found at page 28, line 32.

Claim 29 has been amended to correctly depend from claims which recite a "recombination intermediate."

In addition, Claims 10, 18-20 and 22-24 have been amended to update their dependencies in light of the cancellation of Claims 5, 6, 9 and 27.

All of the amendments are supported throughout the specification and claims as originally filed. For certain claims, specific pages and line numbers where support may be found are provided above. Support for the remaining claims derives from the corresponding claims as originally filed. Accordingly, the amendments do not present new matter and entry is proper.

**Objections to the Drawings and Specification**

The drawings and specification were objected to because drawings appeared to be missing. Two drawing sheets showing Figures 3, 4 and 6 have been provided, rendering the objections moot.

**Objection to Claims**

Claim 1 was objected to because of certain informalities. Specifically, the Patent Office noted that the preamble referred to "an amino acid" but the method steps refer to a

"polypeptide." The preamble has been amended to recite "a polypeptide of interest," as suggested by the Examiner, to provide consistency.

**Non-Statutory Double Patenting**

Claims 5, 10, 15 and 18-20 stand rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over Claims 1-5 and 9 of U.S. Patent No. 6,074,853. Claim 5 has been cancelled and Claims 10, 18-20 and 22-24 have been amended to remove their dependency upon Claim 5. Claim 15 depends from amended Claim 10. Thus, the rejection is moot.

**Rejection of Claims 1-29 Under 35 U.S.C. § 112, Second Paragraph**

Claims 1-29 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The rejections of Claims 5, 6, 9 and 27 are mooted by their cancellation. The rejections of the remaining claims have been overcome by amendment.

Specifically, Claims 1-3 now include the phrase "whereby said first predetermined sequence undergoes domain specific gene evolution" which relates back to the phrase "gene evolution" in the preamble.

Claims 2, 4 and 8 have been amended to include the phrase "or said first library of altered target nucleic acids" in order to clarify the nucleic acids being contacted.

Claims 10 and 11 have been amended to correctly identify the claims from which they depend. Claim 10 has also been amended to delete the phrase "said library of altered target nucleic acids" in favor or "the resultant product" in order to more clearly identify the nature of the product that is being introduced into cells.

Claim 14 has been amended to recite "the variant polypeptides," which finds clear antecedent basis support in the claim from which it depends.

Claim 23 now refers to "said target nucleic acid," which has antecedent basis in the claims from which it depends.

Claim 24 has been amended to delete its dependency upon Claims 7 and 8.

Claim 29 has been amended to delete its dependency upon Claims 1, 2, 5-8, 25, 27 and 28.

Applicant believes the amendments address all of the Patent Office's concerns, and requests that the rejection of Claims 1-29 under 35 U.S.C. § 112, second paragraph, be withdrawn.

**Rejection of Claims 1, 2, 5-14 and 16-29 Under 35 U.S.C. § 102(e)**

Claims 1, 2, 5-14 and 16-29 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Pati *et al.* (U.S. Patent No. 5,948,653). The rejection is moot as applied to canceled Claims 5, 6, 9 and 27 and traversed as applied to amended Claims 1, 2, 7-8, 10-14, 16-26 and 28-29 on the ground that the cited reference fails to teach each and every limitation of the rejected claims.

To anticipate a claim under 35 U.S.C. § 102(e), a reference must teach every element of the rejected claim (MPEP § 2131). According to the Patent Office, Pati *et al.* teaches a method of generating libraries of altered target nucleic acids that comprises combing a target nucleic acid encoding a polypeptide of interest with a recombinase and at least one pair of single-stranded targeting polynucleotides having a homology clamp that targets a domain of a polypeptide of interest. The Patent Office also alleges that, among other things, evolving two or more domains is taught.

All of the rejected claims include the step of repeating the contacting. For example, amended Claim 1 recites "repeating said contacting on said library of altered nucleic acids." Independent Claim 7 also includes such a "repeating" step. The remaining pending rejected claims (Claims 8, 10-14, 16-26 and 28-29) ultimately depend from amended Claim 1 or Claim 7 and therefore also include such a "repeating" step. Pati *et al.* does not teach or suggest such a "repeating" step, and hence, Pati *et al.* does not anticipate these claimed subject matter.

Accordingly, since the cited reference fails to teach each and every limitation of the pending rejected amended Claims, Applicants request that the rejection of Claims 1, 2, 5-14 and 16-29 under 35 U.S.C. § 102(e) be withdrawn.

**Rejection of Claims 1, 2, 5-14 and 16-29 Under 35 U.S.C. § 102(e)**

Claims 1, 2, 5-14 and 16-29 stand rejected under 35 USC § 102(e) as allegedly being anticipated by Zarling *et al.* (U.S. 2002/0090361). The rejection is moot as applied to canceled Claims 5, 6, 9 and 27 and traversed as applied to amended Claims 1, 2, 7-8, 10-14, 16-26 and 28-29 for the reasons discussed above. Like the Pati *et al.* reference, the Zarling *et al.* reference does not teach or suggest the "repeating" step recited in the pending rejected claims. Accordingly, the Zarling *et al.* reference does not anticipate amended Claims 1, 2, 7-14, 16-26 and 28-29. Withdrawal of the rejection of Claims 1, 2, 5-14 and 16-29 is therefore requested.

**Rejection of Claims 1, 2 and 5-29 Under 35 U.S.C. § 103(a)**

Claims 1, 2 and 5-29 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentably obvious over the previously cited Pati *et al.* reference. The rejection is moot as applied to canceled Claims 5, 6, 9 and 27 and traversed as applied to amended Claims 1, 2, 7-8, 10-14, 16-26 and 28-29 on the ground that the Patent Office has failed to establish a *prima facie* case of obviousness.

In rejecting claims under §103(a), the Patent Office bears the burden of establishing a *prima facie* case of obviousness (MPEP § 2142). To establish a *prima facie* case, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference(s) must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed combination *and* the reasonable expectation of success must *both* be found in the prior art, and *not* in Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP §2142.

As mentioned above, all of the pending rejected amended claims require that the contacting step be repeated. The Pati *et al.* reference is silent in this regard; it does not teach or suggest repeating the contacting.

This deficiency is fatal to the rejection. It simply does not matter whether secretion of proteins would have been obvious at the time the instantly claimed inventions were made. The Pati *et al.* reference combined with the Patent Office's reasoning fails to teach each and every limitation of the rejected amended claims. Accordingly, *prima facie* obviousness is not established and the rejection of Claims 1, 2 and 5-29 under 35 U.S.C. § 103(a) should be withdrawn.

It is also noted that of the rejected claims, only amended Claim 14 specifically concerns secretion of the variant polypeptides. Thus, the rejection appears to be inapposite to the other rejected claims. In any event, the rejection fails with respect to all of the rejected claims for the reasons stated above.

**Rejection of Claims 1, 2 and 5-29 Under 35 U.S.C. § 103(a)**

Claims 1, 2 and 5-29 stand rejected as being allegedly unpatentably obvious over the previously-cited Zarling *et al.* reference. Applicant traverses the rejection for the reasons discussed above. Like the Pati *et al.* reference, the Zarling *et al.* reference fails to teach or suggest the repeating step recited in the pending rejected claims. As a consequence, the Zarling *et al.* reference and reasoning provided by the Patent Office fail to render the pending rejected claims *prima facie* obvious. Withdrawal of the rejection of Claims 1, 2 and 5-29 is therefore requested.

**Rejection of Claims 1-14 and 16-29 Under 35 U.S.C. § 103(a)**

Claims 1-14 and 16-29 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentably obvious over the previously-cited Pati *et al.* reference as applied to Claims 1, 2, 5-14 and 16-29, and further in view of Shortle *et al.*, 1980, *Proc. Natl. Acad. Sci.* 77:5375-5379 ("Shortle *et al.*") and Stemmer *et al.*, U.S. Patent No. 5,605,793 ("Stemmer *et al.*"). The rejection is moot as applied to canceled Claims 5, 6, 9 and 27 and traversed as applied to amended Claims 1-4, 7-8, 10-14, 16-26 and 28-29.

As an initial matter, Applicants note that only amended Claim 3 and the claims that depend therefrom (Claims 4, 10-24, 26 and 29) specifically recite the use of a nuclease to nick the recombination intermediate. Amended independent Claim 1 and the claims that depend therefrom (Claims 2 and 25) do not specifically recite this step. Consequently, Applicant believes the instant rejection is inapposite to amended Claims 1, 2 and 25 and germane only to amended Claims 3-4, 10-24, 26 and 29.

The rejection is flawed in several respects. First, it is based upon an incorrect understanding of the teaching of the Stemmer *et al.* reference. At page 10 of the Office Action, the Patent Office states that Stemmer *et al.* teach a method of in vitro homologous recombination utilizing a target nucleic acid and polynucleotides *in which the target nucleic acid is nicked with a nuclease* and then is reassembled and recombined to provide a library of altered nucleic acids. Applicant disagrees.

Stemmer *et al.* teach a recursive method of "DNA shuffling." According to the method, a double-stranded template polynucleotide is incubated with single- or double-stranded nucleic acid fragments having regions of identity and heterology with the template polynucleotide (Col. 6, line 61 through Col. 7, line 5). The template and nucleic acids are then randomly digested into fragments ranging in size from 5 bp to 5 kb (Col. 7, lines 6-11). Additional single- or double-stranded nucleic acid fragments may be added at this step (Col. 7, lines 36-40). Next, the resultant nucleic acids are denatured into single strands, reannealed (Col. 7, lines 63-67) and incubated in the presence of a polymerase and dNTPs to fill in any gaps and synthesize complementary strands (Col. 8, lines 24-28). The cycle of denaturation, reannealing and incubation in the presence of the polymerase and dNTPs is then repeated from, for example, 2-50 times (Col. 8, lines 40-45). The result of this process can be cloned into cells and the "shuffled" proteins expressed (Col. 8, lines 60-61 and Col. 9, lines 12-24).

When read in context, it is clear that the section of Stemmer *et al.* relied upon by the Patent Office to support the passage italicized above (specifically, Col. 7, lines 12-20) merely teaches that a nucleic acid having multiple nicks (presumably to alleviate super-coiling) may be used *as the template nucleic acid* in the above methods:

> Alternatively, it is also contemplated that *double-stranded nucleic acid having multiple nicks may be used in the methods of the invention.*

Col. 7, lines 12-24. This passage *does not* support the Patent Office's conclusion that Stemmer *et al.* teach a method which involves nicking the target nucleic acid with a nuclease. Although Stemmer teaches *digesting* the various nucleic acids into fragments, nowhere does Stemmer teach nicking the nucleic acids as a step of his method.

Nor does Stemmer *et al.* teach "homologous recombination" as that expression is understood by skilled artisans. In the method of Stemmer *et al.*, various polynucleotides having regions of identity and heterology with one another are digested, denatured, annealed and incubated with a polymerase and dNTPs. In contrast, in homologous recombination, the various polynucleotides are not digested or denatured. Rather, strands having certain degrees of homology form complex intermediates which are resolved into the product, typically with the aid of an enzyme such as a recombinase. Thus, while the method of Stemmer *et al.* shares some conceptual similarities with homologous recombination in that it utilizes polynucleotides having regions of identity and heterology, the method *does not* involve homologous recombination in the classic sense.

Shortle *et al.* teach the use of single strand-specific S1 nuclease to nick the single-stranded DNA displaced in a single D-loop recombination intermediate formed between a recombinase, a target nucleic acid and a single-stranded targeting poynucleotide (*see, e.g.,* FIG. 1 at page 5376). According to Shortle *et al.*, once formed, the nicks were converted to short gaps which were then mutagenized specifically with sodium bisulfite.

The teachings of the Pati *et al.* reference were discussed previously.

When the cited references are read in context and accorded their proper teachings, the only way they can be combined to arrive at the methods recited in amended Claims 3-4, 10-24, 26 and 29 is to comb through their various teachings and selectively pick and choose only those portions that support the rejection, ignoring their context and surrounding teachings, and then to combine these selected portions in an arbitrary fashion to attempt to meet the limitations of the claims.

For example, amended Claim 3 recites a method that involves contacting a target nucleic acid with a recombinase and a first pair of single-stranded targeting polynucleotides to form a first recombination intermediate, contacting the recombination intermediate with a single strand-specific nuclease to form a nicked target nucleic acid and reassembling and recombining the nicked target nucleic acid to evolve a first library of altered target nucleic acids.

The only way to combine the cited Pati *et al.*, Shortle *et al.* and Stemmer *et al.* references to attempt to achieve the methods of amended Claim 3 is to start with the teaching of Pati *et al.* to form the recited first recombination intermediate, then to selectively apply that portion of Shortle *et al.* which teaches nicking a recombination intermediate with a single strand-specific nuclease, and then to further selectively apply that portion of Stemmer *et al.* which teaches reassembling and recombining fragmented polynucleotides. Stemmer *et al.* teach reassembling and recombining *a completely different starting material.* Specifically, in the method of Stemmer *et al.*, a plurality of digested polynucleotides are reassembled and recombined. This starting material does not include any recombinases; Stemmer *et al.* simply do not teach or suggest the use of recombinases in their methods. Nor are the polynucleotides of Stemmer *et al.* nicked with a single strand-specific nuclease; they are digested into fragments.

Applying the prior art in such a mosaic fashion, using the Applicants' disclosure as a template and selecting only those teachings that are necessary to support a rejection while ignoring their context and/or other teachings in the same document, constitutes a legally improper "hindsight" reconstruction:

> It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.

*In re Gorman*, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991); *see also, Interconnect Planning Corp.*, 227 USPQ 543, 551 (Fed. Cir. 1985) ("When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself.").

Moreover, the combination of the cited references falls short of claimed methods. Amended Claim 3 recites the use of a recombinase and *a pair* of substantially complementary targeting polynucleotides. As taught throughout the specification, in this context, the recombinase and such pairs of targeting polynucleotides form a double D-loop recombination intermediate with a target nucleic of interest (*see, e.g.*, specification at page 15, lines 19-16, line 28). Shortle *et al.* teach nicking the displaced strand of a *single D-loop* recombination intermediate formed between a target nucleic acid, a recombinase and a single single-stranded targeting polynucleotide (*see, e.g.*, FIG. 1 at page 5376). Shortle *et al.* do not teach or suggest that a double D-loop can be nicked with a single strand-specific nuclease. Pati *et al.* does not teach nicking recombination intermediates with single strand-specific nucleases and Stemmer *et* al. is completely silent regarding the use of recombinases and single strand-specific nucleases.

Thus, the combination of Pati *et al.*, Shortle *et al.* and Stemmer *et al.* fails to teach each and every limitation of the rejected claims. Specifically, the combination fails to teach or suggest nicking the recombination intermediate formed between a target nucleic acid, a recombinase and a *pair* of substantially complementary targeting polynucleotides with a single strand-specific nuclease, as recited in amended Claim 3. As mentioned above, one of the three requirements of a proper *prima facie* obviousness is that the the combination of references relied upon by the Patent Office teach each and every limitation of the rejected claims. Since the combination of Pati *et al.*, Shortle *et al.* and Stemmer *et al.* fail to do so, *prima facie* obviousness has not been established.

Moreover, assuming, *arguendo*, the Shortle *et al.* references teaches nicking of a double D-loop recombination intermediate, which it clearly does not, the Patent Office has failed to provide any rationale as to *why* one of skill in the art would have been motivated to do two things: (1) nick the recombination intermediates of Pati *et al.* with a single strand-specific nuclease; and (2) reassemble and recombine such nicked intermediates according to the methods of Stemmer *et al.* Such a showing regarding motivation is critical to a proper *prima facie* case of obviousness.

According to the Patent Office, motivation is supplied by Stemmer *et al.*, because Stemmer *et al.* teach a "particularly advantageous way to utilize homologous recombination in

generating sequence mutants." Office Action at page 12. However, as discussed previously, Stemmer *et al. do not* teach homologous recombination as that expression is understood by skilled artisans. Rather, Stemmer *et al.* teach a self-contained method of "DNA shuffling" that does not employ recombinases or homologous recombination. The Patent Office has failed supply a rationale as to why one of ordinary skill would have been motivated to modify the teachings of Stemmer *et al.* (or for that matter Pati *et al.* ) in the first place.

The Stemmer *et al.* reference is an issued patent. As such, it enjoys a statutory presumption that it is fully operative. Conspicuously absent from the rejection is an explanation of why one of ordinary skill would have been motivated to modify such fully operative teachings. Why would one of ordinary skill in the art desiring to "shuffle DNA" simply not use the method disclosed by Stemmer *et al.*? Moreover, assuming, *arguendo*, one of ordinary skill decided to modify the methods of Stemmer *et al.*, what would have motivated her to select the specific portions of Shortle *et al.* and Pati *et al.* relied upon by the Patent Office?

Stemmer *et al.* fails to provide such motivation. Motivation is also not found in Pati *et al.* Pati *et al.* does not teach the use of single strand-specific nucleases or reassembling and recombining. Likewise, Shortle *et al.* fails to provide motivation. In addition to the shortcomings of Shortle *et al.* discussed above, in the method of Shortle *et al.*, the nicked recombination intermediates are not reassembled and recombined. Rather, the nicks are converted to small gaps and mutagenized specifically with sodium bisulfite. Indeed, the *only* motivation to piece together the specific teachings of the references relied upon by the Patent Office comes from Applicants' disclosure. As mentioned above, such a hindsight reconstruction cannot carry the Patent Office's burden of establishing proper motivation.

Lastly, assuming once again for the sake of argument, that proper motivation had been supplied, the rejection would still fail. To establish *prima facie* obviousness, the Patent Office also bears the additional burden of showing that one of ordinary skill would have had a reasonable expectation of success. In the instant case, one of ordinary skill could not have reasonably expected that the nicked recombination intermediates could be successfully used as starting materials in the recombining and reassembly taught by Stemmer *et al.* The method of Stemmer *et al.* does not recombine and reassemble recombination intermediates. Instead,

digested polynucleotides are recombined and reassembled. None of the other cited references teach that nicked recombination intermediates can be reassembled and recombined. Accordingly, the reasonable expectation of success necessary to establish a proper *prima facie* case of obviousness is lacking.

For the reasons discussed above, Applicants submit the combination of Pati *et al.*, Shortle *et al.*, and Stemmer *et al.* fails to render amended Claim 3 *prima facie* obvious. All other claims to which the rejection appears germane depend from amended Claim 3. Accordingly, the cited combination fails to render amended Claims 4, 10-24, 26 and 29 *prima facie* obvious, as well. Specifically, the cited combination of references is deficient with respect to each of the three prongs of a proper *prima facie* case of obviousness. Accordingly, since prima facie obviousness has not been established, Applicants request that the rejection of Claims 1-14 and 16-29 under 35 U.S.C. § 103(a) in view of the cited Pati *et al.*, Shortle *et al.*, and Stemmer *et al.* references be withdrawn.

**Rejection of Claims 1-14 and 16-29 Under 35 U.S.C. § 103(a)**

Claims 1-14 and 16-29 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentably obvious over the previously-cited Zarling *et al.* reference in view of the previously-cited Shortle *et al.* and Stemmer *et al.* references.

The rejection is traversed for the reasons discussed above. The teaching of Zarling *et al.* is essentially cumulative to that of Pati *et al.* Thus, none of the deficiencies discussed above is cured by Zarling *et al.* Withdrawal of the rejection of Claims 1-14 and 16-29 for the reasons of record is therefore requested.

**Rejection of Claims 1, 2, 5-14, 16-22 and 24-29 Under 35 U.S.C. § 103(a)**

Claims 1, 2, 5-14, 16-22 and 24-29 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Patten *et al.*, U.S. Patent No. 6,335,160 ("Patten *et al.*") in view of Zarling *et al.*, U.S. Patent No. 5,763,240 ("Zarling II"). The rejection is moot as applied to canceled Claims 5, 6, 9 and 27 and traversed as applied to amended Claims 1, 2, 7-8, 10-14, 16-22, 24-26 and 28-29 on the ground that the Patent Office has failed to establish a *prima facie* case of obviousness. Specifically, the Patent Office has failed to provide any rationale as to why

one of ordinary skill in the art would have been motivated to combine the cited Patten *et al.* and Zarling II references.

As an initial matter, Applicants note that the rejection is based upon a misunderstanding of the Patten *et al.* reference. The Patten *et al.* reference, like the Stemmer *et al.* reference, teaches methods of evolving proteins that employ recombining and reassembling certain polynucleotides. However, like Stemmer *et al.*, Patten *et al.* do not teach or suggest the use of targeting polynucleotides and a recombinase, and hence do not teach or suggest homologous recombination as that expression is understood by skilled artisans.

Presumably, the Patten *et al.* reference is relied upon only for its recursive teaching. However, the Patent Office has failed to provide any rationale as to why one of ordinary skill would have motivated to combine Zarling II with Patten *et al.* The only mention of motivation is directed to the secretion of polypeptides, which the Patent Office explicitly states neither Zarling II nor Patten *et al.* teach. This statement is insufficient to carry the Patent Office's burden of establishing that one of ordinarly skill in the art would have been motivated to combine the teachings of Zarling II and Patten *et al.*

The reality of the situation is that one of ordinary skill would not have been so motivated. As an issued patent, Zarling II enjoys a statutory presumption that it is fully operative. Patten *et al.* provides a similar statutory presumption. There is no motivation or suggestion in Zarling II to apply its teaching recursively. Likewise, there is no motivation or suggestion in Patten *et al.* to use any methods of mutagenesis other than those specifically disclosed, and in particular there is no motivation or suggestion to use the recombinase-mediated homologous recombination method taught by Zarling II. It is well settled that "[t]he mere fact that references *can* be combined or modified does not render their resultant combination obvious *unless the prior art also suggest the desirability of the combination.*" *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990) (emphasis supplied); *see also*, MPEP § 2143.01. In the instant case, the prior art lacks such suggestion or desirability.

Accordingly, Applicants submit the combination of Zarling II and Patten *et al.* fails to render amended Claims 1, 2, 7-8, 10-14, 16-22, 24-26 and 28-29 *prima facie* obvious.

Applicants therefore request that the rejection of Claims 1, 2, 5-14, 16-22 and 24-29 under 35 U.S.C. § 103(a) based upon the combination of these references be withdrawn.

**Rejection of Claims 1-14, 16-22 and 24-29 Under 35 USC §103(a)**

Claims 1-14, 16-22 and 24-29 stand rejected under 35 USC §103(a) as being allegedly unpatentably obvious over the previously-cited Patten *et al.* reference in view of the previously-cited Zarling II reference and further in view of the previously-cited Shortle *et al.* and Stemmer *et al.* references. The rejection is moot as applied to canceled Claims 5, 6, 9 and 27 and traversed as applied to amended Claims 1-4, 7-8, 10-14, 16-22, 24-26 and 28-29 for the same reasons stated in connection with the rejection based upon a combination of Pati *et al.* (or Zarling *et al.*) in view of Shortle *et al.* and Stemmer *et al.* The newly cited Zarling II and Patten *et al.* references do not cure any of the deficiencies of the Pati *et al.*, Zarling *et al.*, Shortle *et al.* and Stemmer *et al.* references discussed previously. Accordingly, the instant rejection should be withdrawn for the reasons of record.

**Conclusion**

Applicants submit that amended Claims 1-4, 7-8, 10-26 and 28-29 satisfy all of the statutory requirements for patentability and are in condition for allowance. An early notification of the same is kindly solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

DORSEY & WHITNEY LLP

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By: Ann M. Caviani Pease
Reg. No. 42,067

Dorsey & Whitney LLP
Four Embarcadero Center, Suite 3400
San Francisco, California 94111-4187
Telephone: (650) 494-8700
Facsimile: (650) 494-8771